MONTH OF BIRTH & CHILDHOOD ASTHMA

By Shadi Mahmoodi

Senior supervisor: Dr. Tim Takaro

ABSTRACT

Background: Studies in the United States and Europe show that children born in fall-winter have higher risk of developing atopic status later in life. This study examines the relationship between month of birth and development of atopic status at 3 years of age across Canada.

Method: The data were obtained from the Canadian Healthy Infant Longitudinal Development (CHILD) study. Data about month of birth, exposure to second hand smoking, mold, pet and cold were extracted from self reported questionnaire. Exposure to Nitrogen dioxide (NO2) was calculated by averaging the concentration of NO2 for the first six month of life for each participant. In total, 2367 children of approximately 3 years of old including 338 atopic individuals that had complete data on date of birth, atopic status and study location were included. The logistic regression run to do bivariate analysis and build the final model.

Results: Results suggest that children born in June and December have higher risk of developing atopic status at three years old, though this result was not significant.

Conclusion: Further research is needed to investigate seasonal pollen pattern and its association with atopic status. These results could be used to implement preventive measures for early management of childhood asthma.

omeed kashefi

Table of Content

Background and Rationale

Introduction

Asthma is a serious chronic disease that can have life threating consequences (Millar & Hill, 1998). Asthma medically is defined as “chronic inflammatory disease of the airways” that can cause shortness of the breath, tightness in the chest, coughing, and wheezing (Asthma Facts & Statistics, 2016, p.1). The respiratory system of people with asthma often overreact to stimuli such as aeroallergen, cold weather and dry air (Millar & Hill, 1998). If left untreated, this induced airway inflammation that can lead to an asthma attack (Asthma Facts & Statistics, 2016).

This chronic lung disease affects over 2 million Canadians, including 10% to 15% of children (Garner & Kohen, 2008). The prevalence of childhood asthma between the ages of 0 to 11 years old has increased from 11% in 1994/1995 to 13% in 2000/2001 according to the National Longitudinal Survey of Children and Youth (NLSCY) (Garner & Kohen, 2008). Although the prevalence of childhood asthma has increased, the proportion of asthmatic children who are experiencing severe asthma attack has dropped from 47% in 1994/1995 to 36% in 2000/2001, possibly due to better management of the disease (Garner & Kohen, 2008).

Asthma and the Quality of Life

Living with asthma has a huge impact on quality of life for children which further affects their adulthood life as well. For example, according to NLSCY 7 % of children between the ages of 0 to 11 who have asthma have fair to poor health status, where this proportion is 1% in children without asthma (Garner & Kohen, 2008). In addition, the same survey shows that childhood asthma lowers children’s physical activity level.

Ten percent of children were described as “less active” compared to 6 % of children without asthma (Garner & Kohen, 2008). Children with asthma also have to go to more doctors visits which further limits their normal lifestyle (Garner & Kohen, 2008). They also experience more hospital admissions (11%) compared to children without asthma (5%). This percentage increases to 19% for children who experienced asthma attacks in 2001(Garner & Kohen, 2008).

Childhood asthma also has long-term consequences that affect the quality of life through adulthood. As discussed above, because of asthma, children may exercise less, research shows even if they outgrow the asthma, the sedentary behaviour will likely to continue. This sedentary behaviour, as a consequence of asthma, can lead to developing obesity, diabetes, and cardiovascular diseases later in life (Fletcher, Green, & Neidell, 2010).

Moreover, having asthma narrows airways which reduces the amount air going to the lungs which can lead to long term damages to the respiratory system (Fletcher, Green, & Neidell, 2010). Additionally, consumption of asthma medication may create adverse effects in some populations which further lowers the quality of life of these individuals (Fletcher, et al., 2010).

Asthma and its burden on society and health care system

Childhood asthma not only affects the individual life, but it also has a huge impact on society and the healthcare system. A comprehensive study in 1996 reported an estimate of $504 million direct and indirect costs of asthma on the Canadian healthcare system (Krahn, Berka, Langlois & Detsky, 1996). They reported that the majority of the the total cost of asthma, 61% or $306 million, was due to the direct cost

of the disease. The largest proportion of direct costs is due to drug costs, followed by hospital inpatient care and physician services (Krahn et al., 1996). The largest proportion of indirect costs is associated with illness related disabilities following by productivity loss related to school (Krahn et al., 1996).

A more recent study in 2010 by the Conference Board of Canada estimated that the cost of the three major chronic lung diseases (including asthma) on the Canadian health care system is $12 billion (The Conference Board of Canada, 2012). It was predicted that if no further preventive strategies were implemented to manage respiratory diseases, the annual economic burden is projected to double by 2030 (The Conference Board of Canada, 2012). Therefore, it is important to study the variety of underlying reasons behind childhood asthma in order to be able to develop effective preventive measures to reduce the burden of this disease on individuals and on society.

Purpose & Argument

In addition to the genetic components and positive family history, environmental factors such as dry weather, air pollution, aeroallergens, viral infections and smoking are major contributors to developing childhood asthma (Gazala, Ron-Feldman, Alterman, Kama, & Novack, 2006).

It has been shown that a significant proportion of children who developed asthma suffered from bronchiolitis in their infancy (Gazala et al, 2006). One possible explanation could be because of the immaturity of an infant's immune system; they are more susceptible to viral lower respiratory infection which can trigger reoccurrence of wheezing and create hypersensitivity (Gazala et al, 2006). Additionally, early exposure to aeroallergens may also trigger hypersensitivity of the respiratory system and lead to

developing wheezing and asthma in children (Karachaliou, Panagiotopoulou, Manousakis, Sinaniotis, & Papageorgiou, 1995). Both exposure to viral respiratory infections and aeroallergens have a seasonal pattern; therefore, literature suggests that there might be an association between the season or the month of birth and developing childhood asthma and wheezing (Clark, Baptist, Ko, Leo, & Song, 2012).

For example, a study in Israel showed that children between the ages of 5 to 7 years who were born between March and June are at higher risk of developing asthma compared to children who were born between October and December (Gazala et al., 2006). One possible explanation offered was that children who were first exposed to Respiratory Syncytial Virus (RSV) later on in their first year of life were at higher risk of developing asthma, compared to those who got exposed in their first months of life (Gazala et al., 2006). Additionally, a study in Melbourne showed that there is an association between exposure to pollen in the first six months of life and aeroallergens sensitization at 2 years old and developing asthma later in childhood (Erbas et al., 2013). In California, a study specifically examined the association between exposure to pollen and fungi during early months of life and developing wheezing at the age of 2 (Harley et al., 2009). They found that children who were born in the fall have the highest risk of developing asthma (Harley et al., 2009). Other studies in Greece and Munich also show an association between the month of birth and developing atopy and asthma in children (Karachaliou et al., 1995; Wjst, Dold, Reitmeir, Stiepel, & Von Mutius,1992).

These studies, along with other ones done across Europe and the United States show that depending on the season or month of birth, there is a window of exposure to RSV and/or pollen or other seasonal factors that can trigger hypersensitivity and the

development of asthma in infants (Clark et al., 2012). Therefore, the focus of this paper is to investigate whether there is any association between month of birth and developing asthma in children across Canada. The results will be used to support preventive strategies that could reduce the burden of this chronic disease on families and the healthcare system outlined in the discussion.

Methods

Data collection:

The data for this paper are extracted from the The Canadian Healthy Infant Longitudinal Development (CHILD) study.

The CHILD study is a national longitudinal birth cohort study that was established in 2008 to address the complex interaction between genetics and the environment in the development of childhood asthma (Takaro et al., 2015). This comprehensive study contains risk assessments for both pre- and post- natal environmental exposure. “Additionally, the design included a comprehensive assessment of relevant family history, psychosocial environment, nutritional factors, infections, genetics, and epigenetics” (Takaro et al., 2015, p.1). See Figure 1.

Study population:

The CHILD study enrolled 3624 pregnant mothers between 2008 and 2012 from four major cities across Canada (Vancouver, Edmonton, Winnipeg and Toronto) (Takaro et al., 2015).

> “Inclusion criteria were age >18 years (>19 years in Vancouver), living in proximity (<50 Km) to a participating delivery hospital, able to read, write and

speak English, willing to donate cord blood, planning to deliver at a designated recruitment center participating hospital, and infant born at or after 35 weeks. Exclusion criteria were major congenital abnormalities or respiratory distress syndrome (RDS), expectation of moving away from a recruitment center within 1 year of recruitment, children of multiple births or resulting from in vitro fertilization, and children not spending over 80% of time in the index home" (Takaro et al., 2015, p.2).

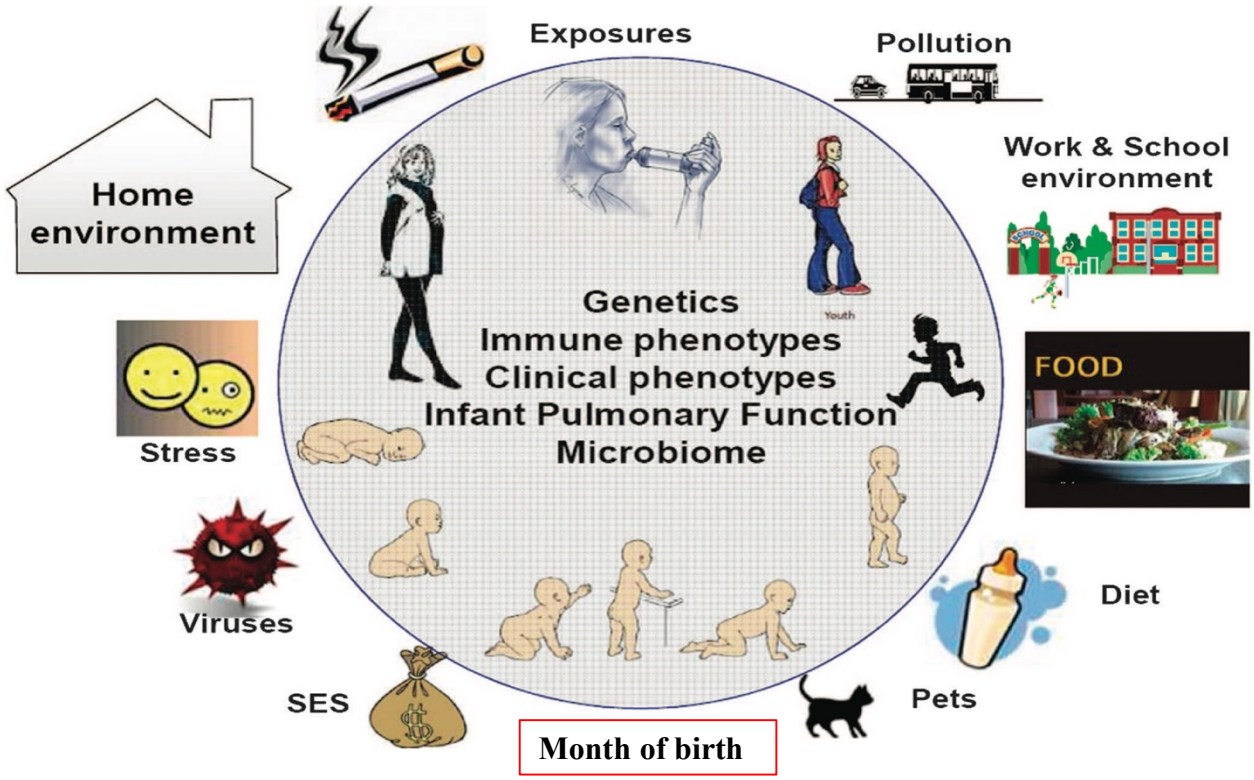

Figure 1. Interacting risk factors measured in the CHILD study, including multiple environmental, infective, nutritional and psychosocial exposures; genetics; lung function; and microbiome, resulting in immunological and clinical phenotypic outcomes.

Source: Takaro, T. K., Scott, J. A., Allen, R. W., Anand, S. S., Becker, A. B., Befus, A. D . CHILD study investigators. (2015). The Canadian healthy infant longitudinal development (CHILD) birth cohort study: Assessment of environmental exposures. Journal of Exposure Science & Environmental Epidemiology, 25(6), 580. doi:10.1038/jes.2015.7

Defining variables:

Outcome Variable: Atopic Status

I chose to assess the atopic status of children at the age of three because the data collection had been completed for this age group. In addition, research has shown that atopy, along with persistent wheezing, at age of 3 could be a predict >65% of the

risk of asthma in children and it is associated with developing asthma in adulthood (Arrieta et al., 2015)

Skin-prick tests were administrated for every subject at approximately the age of 3. The tests were done for the following six inhalant allergens [Alternaria alternata, cat hair, dog epithe- lium, house dust mites (Dermatophagoides pteronyssinus and D. farinae), and German cock- roach] and four food allergens [whole cow's milk, egg white, soybean, and peanuts]. Histamine 1 mg/mL and glycerin were used as positive and negative controls respectively (Sbihi et al., 2015).

For each allergen, I averaged the length and width of the wheal, and defined atopic status where a subject has a positive skin test (> 2mm) to any allergens. Also, following CHILD protocol, I included all the participants with a positive response to histamine and no response to glycerin as atopic.

Questionnaires and home inspection:

In this paper I examine the association between month of birth and developing atopic status at 3 years of age. The information about the subjects' date of birth and sex were derived from the Child Birth Chart Data (CBIRTHCD_107) questionnaire, see Appendix1.

To examine the socioeconomic status, the following three measurements were used: mother's and father's education and the reported household income. This information was derived from the 18 weeks' questionnaire (SES18WK_100), see Appendix1.

As has been discussed above, there is a window of exposure to different environmental factors, such as viral infection and/ mold, that can trigger the development of asthma in children as they age. Therefore, in this paper, I looked at five variables (viral infection, visible mold, exposure to air pollution, exposure to smoking and pet) in the first 6 months of life.

Exposure to air pollution

In this paper, I calculated the average of exposure to nitrogen dioxide (NO2) for the first six month of life for each participant. It has been shown that the average of NO2 concentrations is a good indictor for assessing air pollution exposure (Sbihi et al., 2015). The data on the average of daily NO2 concentration from 2010 to 2013 were downloaded for the four cities of Vancouver (Envitech LTD, 2016), Toronto (Air Pollutant Data, 2016), Edmonton (Airdata | AEMERA, 2016) and Winnipeg (Envitech LTD, 2016). For each day in that time frame the average of the past six months of NO2 concentrations were calculated. This data was merged with the final dataset based on the date on which each participant turned six months.

Exposure to smoking, pets, and mold

Information on exposure to second hand smoke and whether the family owned a pet for the first six months of life for each participants was derived from the self reporting questionnaire (Home Environment 6 Months, HENV6M_165), see Appendix1. I considered subjects to have been exposed to second hand smoke if their parents reported that children were exposed to tobacco smoking at home or away from home.

The information about exposure to visible mold was derived from the home assessments (Environmental Assessment, ENVRA3M_117) that were collected by technicians when the infants were 3 months of age, see Appendix1.

Information on viral infections was derived from the self reporting questionnaire (Child Health 6 Months, CHLTH6M_234) where parents were asked about whether their infants had a cold in the first six months of life, see Appendix1.

Analysis

The analysis was performed in the R studio (R Core Team ,2014). The final logistic regression model was: Atopic status ~ month of birth + sex + pet + mold + mothers' education + income + study center

Before analysing the association between month of birth and developing atopic status, I assessed separately the bivariate associations between atopy and the following environmental factors: exposure to NO2, pets, mold, second hand smoking and study center; parental factors: mother's and father's education and house hold income; and a biological factor: sex. After analyzing the bivariate associations with each of those covariates, the ones that were significate predicators ($p < 0.2$) of the outcome (atopic status) were considered to be included in the final model of month of birth and atopy. I performed a manual stepwise backward regression analysis by removing each variable from the model and chose the best model that explained the majority of the deviance with the lowest Akaike Information Criterion (AIC). The final model contains exposure to mold, pets, subjects' sex, household income and maternal education. The p values for

the other variables (father's education, cold and exposure to NO2, and tobacco smoke) were higher that 0.2; therefore, those variables were excluded from the final model.

Results

Population characteristics and atopy:

Atopy data were examined for 2984 subjects that had the skin- prick test administrated at the age of 3 years old. Two subjects with a positive response to the negative control were excluded, and 17 subjects were removed that had no response to the positive control. In total, 375 children had a positive response to at least one of the ten tested allergens. The data for atopy was merged with the data on date of birth and 11 subjects were removed because their date of birth was missing. Another 77 subjects were removed because of missing data for the study location. The data for the study location were necessary in order to merge the NO2 concentration based on each subjects' city. In total, 2367 subjects including 338 atopic individuals that had complete data on date of birth, atopic status and study location were analyzed, see Table 1. Out of 2367 subjects, 53% were male and 47% were female, 338 (14%) children had positive response to any allergens by the age of three, see Table 1. Vancouver had the largest proportion (20%) of children with atopic status, which is statistically significant compared to Winnipeg (7%) (p value < 0.05), see Table 1. Toronto and Edmonton had the same proportion of atopic children (both 16%), which are statistically significant compared to Winnipeg (p value < 0.05). And Winnipeg had the smallest proportion of children with atopy (7%), Table 1, and Figure 2.

Table 1: Proportion of children with atopic status in each study location.

Study Location	Number of subjects without atopic status	Number of subjects with atopic status(%)	OR (95% CI)
Winnipeg	709	53 (7)	Reference level
Vancouver	425	108 (20)	3.51 (2.45, 5.07)
Toronto	441	89 (16)	2.76 (1.92, 4.02)
Edmonton	454	88 (16)	2.45 (1.66, 3.66)
Total	2029	338 (14)	

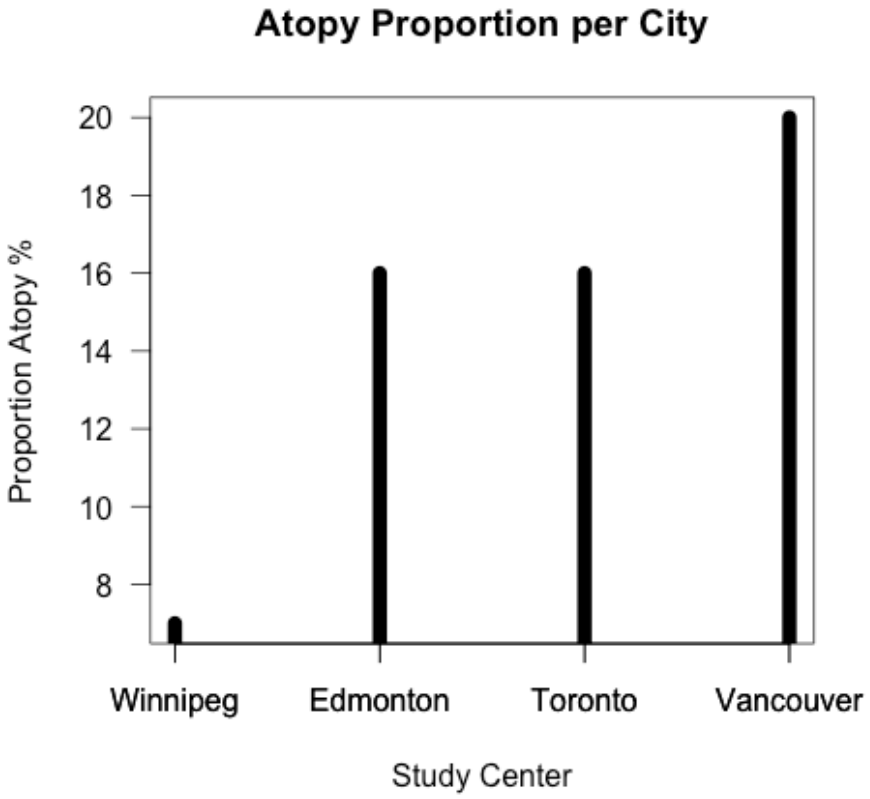

Figure 2: Atopy proportion per city

A bivariate analysis was done on the covariates that were considered for the analysis between month of birth and atopy , see Table 2. Among all the children with atopic status, 62% were males and only 38% were females [odds ratio (OR) = 0.64;

95% confidence interval (CI) : 0.59, 0.83], Table 2. Both parents were highly educated close to 74% had some college or university education, see Table 2. Only the association between maternal education and atopic status in children was significant [College or University education OR = 1.92($p < 0.05$); Postgraduate education OR = 2.35 ($p < 0.05$)], see Table 2. Household income was also associated with atopic status in children but at a lower significant level ($p < 0.2$), see Table 3.

Environmental exposure and association with atopy

Analysis of environmental covariates showed that non atopic participants were more likely to live in a home with pets [OR = 0.62; 95% , CI : 0.47, 0.82] compared with children with atopy, see Table 2. And atopic participants were more likely be exposed to visible mold [OR = 2.01; 95%, CI : 1.32, 2.99] compared with children without atopy, see Table 2. Compared to participants without atopy, atopic children were more likely to get cold and less likely to be exposed to second hand smoking, but these results were not significant ($p > 0.7$). And the association between the average of NO2 concentration for the first six-month life and atopy was not significant ($p > 0.7$).

Table 2: Cohort characteristics and comparison of children with atopic status with children without atopy.

Characteristics	**n (%)**	**Non- atopic**	**Atopic**	**OR (95% CI)**
Personal covariates				
sex				
Male	1134(53)	948(51)	186(62)	
Female	1023(47)	908(49)	115(38)	0.64 (0.50, 0.83)

Socioeconomic covariates				
Maternal Education				
High School	155(7)	143(8)	12(4)	Reference level
College or University	1525(73)	1313(73)	212(73)	1.92(1.093, 3.72)
Postgraduate education	413(20)	345(19)	68(23)	2.35(1.28, 4.68)
Missing	64	55	9	
Paternal Education				
High School	287(14)	253(14)	34(12)	Reference level
College or University	1456(70)	1239(69)	217(74)	1.30(0.89, 1.95)
Postgraduate education	335(16)	293(16)	42(14)	1.06(0.66, 1.74)
Missing	79	1	8	
Household income (CAN $)				
<40,000	137(7)	123(8)	14(5)	Reference level
40,000 – 80,000	446(23)	393(24)	53(20)	1.18(0.65, 2.29)
80,000 – 150,000	847(45)	724(44)	123(47)	1.49(0.86, 2.79)
>150, 000	470(25)	396(44)	74(47)	1.64(0.92, 3.13)
Missing	257	220	37	
Environmental covariates				
Pets				
Yes	797(43)	711(44)	86(33)	0.622 (0.47, 0.82)
No	1069(57)	895(56)	174(67)	
Missing	291	250	41	
Visible Mold				
Yes	168(12)	133(11)	35(19)	2.01(1.32, 2.99)
No	1269(88)	1122(89)	147(81)	
Missing	720	601	119	
Tobacco_ Smoke				
Yes	301(14)	261(14)	40(13)	0.94(0.64, 1.32)
No	1855(86)	1594(86)	261(87)	
Missing	1	1		

Cold				
Yes	1574(82)	1341(82)	233(84)	1.15(0.83, 1.64)
No	343(18)	298(18)	45(16)	
Missing	240	217	23	

Month of birth and association with atopy

The proportions of children with atopy were calculated for each month, see Figure 3. The highest proportion of atopy was for children who were born in November and lowest for children who were born in August. I conducted a bivariate analysis to examine the association between any month of birth and developing atopic status. Results suggested that compared to children born in August, children who born in months of June, July, November and December are more likely to develop atopy ($p < 0.05$), see Table 3.

After examining the monthly results suggesting that there are high proportion of children with atopy in a single summer month (June) and a winter month (December) I wished to see whether a summer (Jun, July, August)-winter (December, January, February) analysis would show any differences between those two seasons. Results showed that the proportion of atopic children born in summer (0.15) is higher compared to children born in winter (0.13), see Table 4. The bivariate analysis for season of birth (summer vs. winter) and atopic status suggested that children born in winter are less likely to develop atopy compared to children born in summer though this was not significant, see Table 4.

To investigate whether the above association between season of the birth and atopy would be different depending on the participants' city of born, I stratified the data

based on the study location. Results suggest that in Edmonton and Toronto, children who were born in winter are more likely to develop atopy compared to children who were born in summer. While in Vancouver and Winnipeg, children who were born in winter are less likely to develop atopy compared to children who were born in summer though this result was not significant see Table 5.

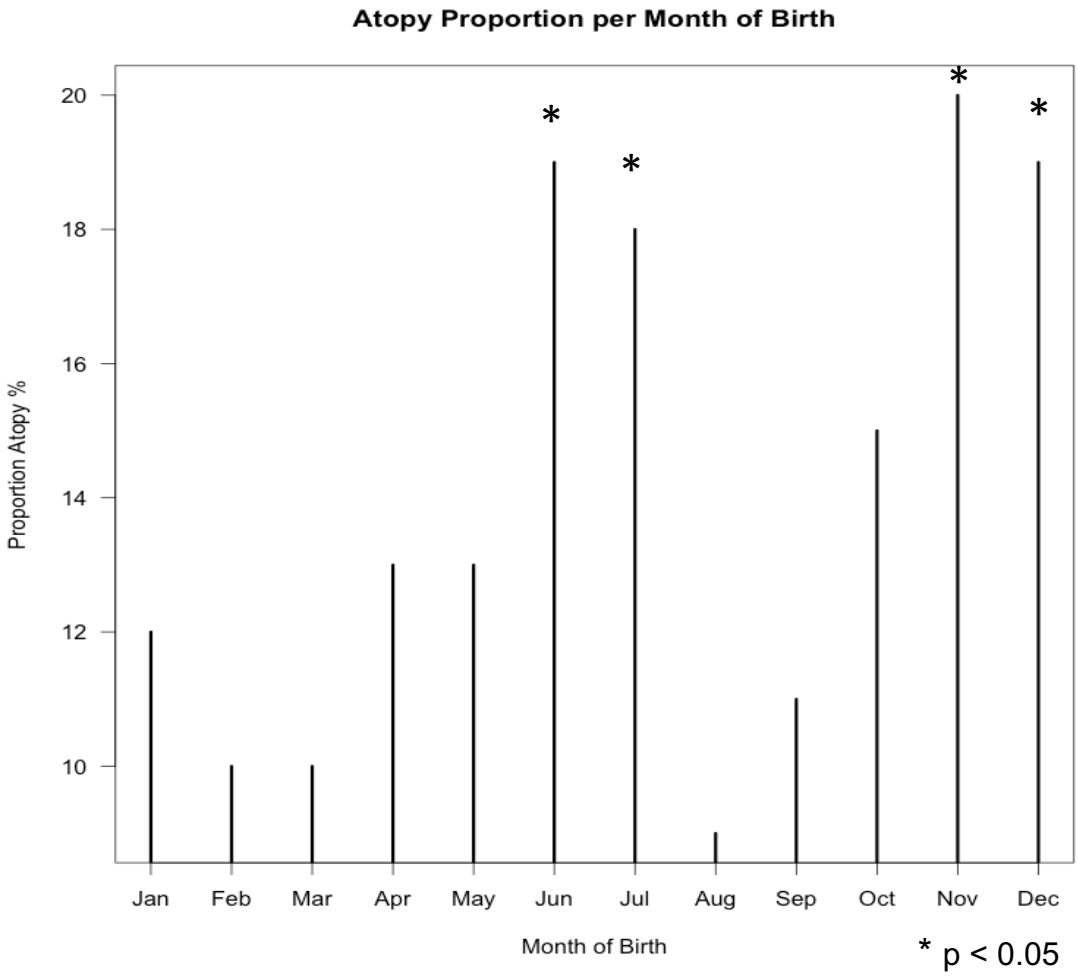

Figure 3: Proportion of children with atopy based on their month of birth

Table 3: Month of birth and it association with atopy.

Month of birth	OR(CI)	P value
Aug	Reference level	
Jan	1.32 (0.71, 2.48)	0.380
Feb	1.05 (0.48, 2.19)	0.890
Mar	1.09 (0.56, 2.10)	0.789
Apr	1.50 (0.63, 2.78)	0.195
May	1.47 (0.97, 2.89)	0.193
Jun	2.20 (1.28, 3.89)	0.005 **
Jul	2.09 (1.19, 3.75)	0.011 *
Sep	1.17 (0.60, 2.27)	0.647
Oct	1.74 (0.91, 3.32)	0.094 .
Nov	2.37 (1.26, 4.50)	0.007 **
Dec	2.33 (1.19, 4.53)	0.013 *

Signif. codes 0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1

Table 4: Season of birth (summer vs. winter) and it association with atopy.

Month of birth	Non- atopic	Atopic	Proportion of atopic children (%)	OR (95% CI)
*Summer	585	106	15.3%	Reference level
*Winter	361	55	13.3%	0.84 (0.59,1.19)

*Summer (Jun, Jul, Aug) Winter (Dec, Jan, Feb)

Table 5: Season of birth (summer vs. winter) and it association with atopy stratified based on each study center.

Study Location	Season of birth	OR (95% CI)
Vancouver	Summer	Reference level

	Winter	0.63 (0.33,1.17)
Toronto	Summer	Reference level
	Winter	1.75 (0.86, 3.68)
Edmonton	Summer	Reference level
	Winter	2.31 (0.11, 24.68)
Winnipeg	Summer	Reference level
	Winter	0.86 (0.36, 2.06)

*Summer (Jun, Jul, Aug) Winter (Dec, Jan, Feb)

Adjusted association between month of birth and atopic status.

To examine the association between month of birth and atopic status, I adjusted the model for covariates (sex, mold, pet, maternal education, income and study location) that had significant association ($p < 0.1$) with the outcome variable (atopic status). After adjusting for the above covariates, Model 1 suggested that children born in June, November and December are more likely to develop atopy compared to children born in August (p value < 0.05).

I built Model 2, by excluding income as it wasn't significant in model 1, see Table 6. Model 2 also suggested that children born in June, November and December are more likely to develop atopy compared to children born in August (p value < 0.05).

To select the best model, first their Akaike Information Criteria (AIC) was compared to understand which model best describes the models' residuals, see Table 6 (Wagenmakers & Farrell, 2004). Based on AIC, Model 1 had the lowest AIC see Table 7.

Based on the best model: Atopy~ Sex+ Mold+ Pet+ maternal education+ Month of birth+ Income + study center, after adjusting for sex, maternal education, household income, exposure to mold and pets and study center, children who born in June, November and December are more likely to develop atopic status (p value < 0.05).

Table 6. Logistic regression models to predict atopic status in children.

Models	**AIC**
Model 1) Atopy ~ Sex+ Mold+ Pet+ Maternal Education+ Month of Birth+ Income+ Study center	810
Model 2) Atopy ~ Sex+ Mold+ Pet+ Maternal Education+ Month of Birth + Study Center	895

Table 7 :Model 1: Atopy ~ Sex+ Mold+ Pet+ Maternal Education+ Month of Birth+ Income+ Study center

Covariates	**Odds Ratio (OR)**	**95 % Confidence Interval**
Intercept	Reference level	
Sex (female)	0.61	0.42 , 0.89
Visible Mold (Yes)	1.57	0.91 , 2.64
Pet (Yes)	0.50	0.33 , 0.72
Maternal Education		
College or University	8.05	1.67, 145.5
Postgraduate education	11.22	2.20, 205.5
Income		
40,000 – 80,000	0.87	0.32 , 2.84
80,000 – 150,000	0.78	0.29 , 2.48
>150, 000	0.70	0.25 , 2.32
Month of Birth		

Jan	2.10	0.79 , 5.59
Feb	1.08	0.31 , 3.38
Mar	1.24	0.46 , 3.28
Apr	1.46	0.57 , 3.78
May	1.33	0.55 , 3.31
Jun	2.97	1.37 , 6.86
Jul	1.84	0.80 , 4.44
Sep	1.16	0.37 , 1.71
Oct	1.87	0.32 , 3.34
Nov	3.69	1.38 , 9.98
Dec	5.02	1.91 , 13.57

Discussion

Month of Birth and Atopy

In this paper, I examined the association between month of birth and developing atopic status at the age of three. Results showed that the highest proportion of children with atopic status at age of three had birth month of June and November, see Figure 3. And children who born in months of June, July, November and December are more likely to develop atopy compared to children who born in August. These results are similar to results found in a case-control study in Beer-Sheva, in Israel, where they found that children born in June have a higher risk of developing asthma (Gazala et al., 2006). These investigators showed that children born in the months of June are more likely to be exposed to pollens and December to RSV compared to children born in other months (Gazala et al., 2006). Another longitudinal study in California showed that there is a seasonal pattern in fungal and pollen spore distribution (Harley et al., 2009). They showed that children born in fall-winter who were exposed to pollen in the first

three month of life, had higher risk of developing wheezing and atopy at the age of 2 (Harley et al., 2009). These early exposures to pollen/ or RSV can increase hypersensitivity in children that will ultimately lead to development of atopy later in life (Clark et al., 2012).

Figure 3 shows that August has the lowest proportion of atopic children. Generally, across Canada, in August we have higher temperature, and research shows that bacteria growth will stop at temperatures higher that 30 °C (PietikÃ¥inen, Pettersson, & BÃ¥Ã¥th, 2005). Therefore, the small proportion of atopic children in August could suggest that children born in this months had lower exposure to bacteria compared to other months. Further research is needed to investigate the pattern of bacteria growth and its association with atopic status across different regions of Canada.

In terms of physical location, the results suggest that Vancouver has the highest proportion of atopy and Winnipeg has the lowest. Vancouver has mild winter and higher humidity, while Winnipeg has longer and colder winter with lower humidity (Chan-Yeung et al., 1995). Research suggests that extreme cold weather inhibits fungi growth, while humidity provides optimal condition for their growth (Talley, Coley, & Kursar, 2002). Higher growth rate of fungi in mild Vancouver climate and longer exposure to fungi could explain the high proportion of atopic children in this city compared to Winnipeg, especially when considering home conditions. Interestingly, a Canadian study compared Vancouver and Winnipeg home conditions to investigate the house mite allergens level (Chan-Yeung et al., 1995). They found that homes in Vancouver have

higher indoor humidity and they found the level of mite allergens were lower in Winnipeg (Chan-Yeung et al., 1995).

Environmental factors and Atopy

Exposure to second hand smoke

Exposure to passive smoking and parental smoking has been linked to an increased risk of developing lower respiratory infections in infancy, which further increases the risk of developing atopy (Jones et al., 2011). However, our results did not show any significant association between exposure to second hand smoke and developing asthma. One possible explanation is that, in this study population, the number of parents who were smokers was low (n = 301, 14 %); therefore, no association between exposure to second hand smoke and development of atopic status in children was detected. Self reported questionnaires for assessing children exposure to second hand smoke can be unreliable due to the social desirability bias (Boyaci et al., 2006). Measurement of the cotinine level - biomarker for tobacco smoke- in children' urine sample provide more accurate estimation of their exposure to second hand smoke (Boyaci et al., 2006). Therefore, our results are likely an underestimate of the true association between exposure to second hand smoke and development of atopic status.

Exposure to visible mold

There appears to be an association between exposure to indoor mold and development of atopy in children. These results are similar to results found in a study

performed in Ohio, where they found that children who were exposed to indoor mold during their infancy had a higher risk of developing atopy at 7 years old (Reponen et al., 2012). Similar to that study, our results showed that children who were exposed to indoor mold during the first three month of life, have a significantly higher risk of developing atopy at the age of three.

A study in Chicago suggested that increased growth rate of mold spore in spring is associated with increased asthma hospitalization (Targonski, Persky, & Ramekrishnan, 1995). They suggested that these small mold spore can exacerbate developing asthma by interacting with other allergens and pollutants (Targonski, et., 1995). More research about the seasonal pattern of mold formation is needed to investigate this association in Canada.

Exposure to pets

Results of our study show that children who live in a home with a pet in their first six months of life, were less likely to develop atopy at the age of three. It has been shown that there is a negative association between dog ownership and developing asthma in children who are born in families without a history of atopic diseases (Pohlabeln , 2016). While having a dog can exacerbate the risk of developing asthma in children who have a positive atopic family history (Pohlabeln, 2016).

Exposure to NO2

Our results from this study did not show any association between average of NO2 concentration in the first six months and development of atopy. While, a

prospective birth cohort study, showed that children who were exposed to traffic-related air pollution (TRAP) during their first year of life have higher odds of developing asthma later in life (Zhou et al., 2013). This could be that because of the small sample size of our study population for, the association between air pollution and atopy was not detected or that the exposure estimate did not have adequate precision.

Viral infection:

Results from this study did not show any association between getting a cold in the first six months of life and developing atopy at the age of three. While, other studies showed that early exposure to a viral infection stimulates a hypersensitivity that could exacerbate the development of asthma in children (Gazala et al, 2006). In addition, a longitudinal study in Tennessee showed as well that the seasonal birth pattern for asthma is overlapped with winter viral infection pattern (Wu et al., 2008). The reason that we did not detect any association between viral infection and developing atopic status could be due to small sample size of our study population.

Biological factors and Atopy

Results show that male participants are more likely to develop atopy. This has been shown in other studies, that boys are more susceptible to developing childhood asthma (Garner & Kohen, 2008). Based on the data from the National Longitudinal Survey of Children and Youth (NLSCY), in 2000/ 2001, 16 % of boys were reported to develop asthma compared to girls where the percentage was 11% (Garner & Kohen, 2008).

Socioeconomic status and Atopy

Children of families with a higher household income had higher risk of developing atopy, though this result was not significant. The NLSCY survey showed that the prevalence of asthma was similar across the income gradient (Garner & Kohen, 2008). Similar studies across Europe also found no association between SES and an asthma diagnosis in children (Garner & Kohen, 2008).

Policy Implication

Knowing that the month of birth impacts the risk of developing atopic status allows healthcare provides and policy makers to provide more support and education to parents. For example, knowing that children who are born in June may have a higher risk of developing atopy can help to raise parents' awareness of exposure to environmental factors and it's affects in the early months of life. For example, parents can check their home ventilation to reduce indoor mold formation. In addition, they can reduce exposure to second hand smoke by eliminating tobacco smoking at home.

In terms of addressing the differences in risk of developing atopic status based on physical location, targeted community based asthma clinic could provide additional education and support to families. For example, in the UK nurse-run asthma clinics within communities have been piloted to assess a patients' health status and provide them with relevant educational resources, such as proper use of inhalator and drug

management (Dickinson, Hutton, Atkin & Jones, 1997). Results showed that these nurse-run asthma clinics reduced the burden morbidity associated with asthma (Dickinson, 1997). Similar nurse-run asthma clinics can be considered to be established here in Canada, especially now that the number of nurse practitioner is rising and we have more nurses available to provide community based services (McMaster Health Forum, 2016).

Providing more education about management of childhood asthma to parents can help to make an informed decision regarding their children's health. Creating more user friendly and accessible information will help parents to easily access good quality information. A study in the UK showed that parents who participated in health educational programs about childhood asthma management did better in the management of asthma and asthma attacks compared to parents that did not participate (Clark et al., 1986). Interestingly, children of parents who attended the educational program reported to be less worried about the limitations that having asthma might impose, such as managing an inhalator (Clark et al., 1986). This ultimately positively impacts children's mental health, which is a very important aspect of their wellbeing.

As was discussed above, exposure to mold significantly increases the risk of developing atopy in children. Therefore, proper ventilation in homes will help to reduce humidity and prevent mold formation should be promoted (Tang, Kuehn, & Simcik, 2015). Encouraging systematic ventilation check as part renting or buying home procedure may help to reduce exposure to indoor mold.

As has been discussed for several exposures in this paper, my findings suggest there is likely to be windows of vulnerability to exposure of environmental factors such as mold, RSV, and pollen that promotes the development of hypersensitivity in infants. The findings here suggest that the the first few months of life should be the focus of promoting preventive measures for childhood asthma.

Preventive measures will help to reduce the burden of the disease on the health care system by reducing hospital admissions. Taking those preventative measurements will also help to reduce the burden of the disease on the individual and families by having the necessary skills to manage the disease. This ultimately will help society by reducing the cost of asthma care, morbidity and mortality including medication and other health care costs and days absent from school or work for both children and their parents.

Limitations

Although the combination of persistent wheezing and atopic status was a better indicator of childhood asthma, the sample was too small for a meaningful analysis (n = 100). Therefore, for a more robust analysis, I chose the atopic status as my outcome variable. Atopy is not as precise a predictor for asthma risk as the combined indicator.

I did not consider all other possible confounding variables, such as data on diet, prenatal exposure or other environmental exposures at home in this study. In addition, there are limitations associated with the Traffic Related Air Pollution (TRAP) measures. In this study, I only included the average of exposure to NO2 in the first six month of life, for more accurate measurements, consideration of the time participants spent outdoor

or indoor will gave a more robust measurement of TRAP. This is due to the limitation of the availability of the data and the scope of this project.

The analysis for this study was done for combined data from all four study centers across Canada (Vancouver, Toronto Edmonton, and Winnipeg) due to small sample size. Only the analysis for birth season and atopy was stratified based on each study center. Result suggested that the association between birth season and atopy was different based on the study location. Therefore, for future studies, to investigate the association between month/ season of the birth and atopy, it is important to stratified the results based on each city to account for differences between different regions of Canada.

Analysis of the seasonal pollen distribution and pattern within each city would have created a clearer understanding of the association between month of birth and childhood asthma. That analysis was beyond the scope of this project and could be considered as a follow up study to complement this preliminary analysis of assessing the relationship between month of birth and childhood asthma.

Reflection

This project was a great learning experience for me. I had the opportunity to investigate an important public health issue, childhood asthma and its implications for society and the healthcare system. As a future public health practitioner, I learned the importance of spending time to understand a public health issue and its impact on the population from different angles. For example, it is very important to understand the

short term and long term impact of childhood asthma on a person's life to be able to develop effective preventative strategies.

In addition, I experienced from the beginning how to form a research question and evaluate available resources to analysis the data and interpret the patterns. I applied the skills that I gained through my course work to complete this project. For example, I used analytic skills that I learned in my epidemiology and statistics classes to clean and analyze the data and understand the patterns of the data. The important part of this paper was to be able to link the findings to develop policy that could improve population health. I really enjoy linking the statistical analysis and patterns to something meaningful that could possibly benefit the society.

Soon, I will start my career in a field of public health, and this project was a great experience to give me the confidence that I am ready to take my learning throughout the past two years and apply it in real life situations.

Acknowledgement

This paper has done with the great support of Dr. Tim Takaro throughout the duration of the project. I would also like to acknowledge the help of Jordan Brubacher, Jaclyn Park, Cecilia Sierra Heredia, Michelle Jones and Yayuk with analysis section. In addition, I would like to thank CHILD study team for giving me the opportunity to work on this project.

References

Airdata | AEMERA. (2016). Airdata.aemera.org. Retrieved 25 May 2016, from http://airdata.aemera.org/aemeraContent/Reports/DataDownloadMain.aspx

Air Pollutant Data. (2016). Airqualityontario.com. Retrieved 25 May 2016, from http://www.airqualityontario.com/history/

Arrieta, M., Stiemsma, L. T., Dimitriu, P. A., Thorson, L., Russell, S., Yurist-Doutsch, S.. the CHILD Study Investigators. (2015). Early infancy microbial and metabolic alterations affect risk of childhood asthma. Science Translational Medicine, 7(307), 307ra152-307ra152. doi:10.1126/scitranslmed.aab2271

Asthma Facts & Statistics. (2016). asthma.ca. Retrieved 16 May 2016, from http://www.asthma.ca/corp/newsroom/pdf/asthmastats.pdf

Boyaci, H., Etiler, N., Duman, C., Basyigit, I., & Pala, A. (2006). Environmental tobacco smoke exposure in school children: parent report and urine cotinine measures. Pediatrics International, 48(4), 382-389. http://dx.doi.org/10.1111/j.1442-200x.2006.02225.x

Chan-Yeung, M., Becker, A., Lam, J., Dimich-Ward, H., Ferguson, A., Warren, P.. . Manfreda, J. (1995). House dust mite allergen levels in two cities in canada: Effects of season, humidity, city and home characteristics. Clinical and Experimental Allergy : Journal of the British Society for Allergy and Clinical Immunology, 25(3), 240-246. doi:10.1111/j.1365-2222.1995.tb01035.x

Clark, N. M., Baptist, A. P., Ko, Y., Leo, H. L., & Song, P. X. K. (2012). The relationship of season of birth to asthma and allergy in urban african american children from 10 to 13 years of age. Journal of Asthma, 49(10), 1037-1043. doi:10.3109/02770903.2012.739239

Clark, N. M., Feldman, C. H., Evans, D., Duzey, O., Levison, M. J., Wasilewski, Y., & ...

Mellins, R. B. (1986). Managing better: children, parents, and asthma. Patient Education And Counseling, 8(1), 27-38.

Cuesta-Herranz, J., Barber, D., Blanco, C., Cistero-Bahíma, A., Crespo, J. F., Fernández-Rivas, M., & ... Tabar, A. I. (2010). Differences among pollen-allergic patients with and without plant food allergy. International Archives Of Allergy And Immunology, 153(2), 182-192. doi:10.1159/000312636

Dickinson, J., Hutton, S., Atkin, A., & Jones, K. (1997). Reducing asthma morbidity in the community: the effect of a targeted nurse-run asthma clinic in an English general practice. Respiratory Medicine, 91(10), 634-640.

Envitech LTD, I. (2016). Envista - Air Resources Manager. Envistaweb.env.gov.bc.ca. Retrieved 25 May 2016, from http://envistaweb.env.gov.bc.ca/

Envitech LTD, I. (2016). Envista - Air Resources Manager. Web31.gov.mb.ca. Retrieved 25 May 2016, from http://web31.gov.mb.ca/EnvistaWeb/Default.ltr.aspx

Erbas, B., Lowe, A. J., Lodge, C. J., Matheson, M. C., Hosking, C. S., Hill, D. J.. . Dharmage, S. C. (2013). Persistent pollen exposure during infancy is associated with increased risk of subsequent childhood asthma and hayfever. Clinical & Experimental Allergy, 43(3), 337-343. doi:10.1111/cea.12071

Fletcher, J., Green, J., & Neidell, M. (2010). Long term effects of childhood asthma on adult health. Journal Of Health Economics, 29(3), 377-387. http://dx.doi.org/10.1016/j.jhealeco.2010.03.007

Garner, R., & Kohen, D. (2008). Changes in the prevalence of asthma among canadian children. Health Reports, 19(2), 45.

Gazala, E., Ron-Feldman, V., Alterman, M., Kama, S., & Novack, L. (2006). The association between birth season and future development of childhood asthma. Pediatric Pulmonology, 41(12), 1125-1128. doi:10.1002/ppul.20442

Harley, K. G., Macher, J. M., Lipsett, M., Duramad, P., Holland, N. T., Prager, S. S.. . Tager, I. B. (2009). Fungi and pollen exposure in the first months of life and risk of early childhood wheezing. Thorax, 64(4), 353-358. doi:10.1136/thx.2007.090241

Karachaliou, F. H., Panagiotopoulou, K., Manousakis, M., Sinaniotis, K., &

Papageorgiou, F. (1995). Month of birth, atopic disease, and sensitization to common aeroallergens in greece. Pediatric Allergy and Immunology : Official Publication of the European Society of Pediatric Allergy and Immunology, 6(4), 216-219. doi:10.1111/j.1399-3038.1995.tb00289.x

Krahn, M. D., Berka, C., Langlois, P., & Detsky, A. S. (1996). Direct and indirect costs of asthma in canada, 1990. Canadian Medical Association Journal, 154(6), 821-831.

Jones, L. L., Hashim, A., McKeever, T., Cook, D. G., Britton, J., & Leonardi-Bee, J. (2011). Parental and household smoking and the increased risk of bronchitis, bronchiolitis and other lower respiratory infections in infancy: Systematic review and meta-analysis. Respiratory Research, 12(1), 5-5. doi:10.1186/1465-9921-12-5

McMaster Health Forum. (2016). Mcmasterhealthforum.org. Retrieved 21 July 2016, f rom https://www.mcmasterhealthforum.org/docs/default-source/Product-Documents/issue-briefs/nurse-practitioners-in-primary-healthcare-in-canada-ib.pdf?sfvrsn=2

Millar, W. J., & Hill, G. B. (1998). Childhood asthma [1978/79 to 1994/95 data]. *Health Reports, 10*(3), 9-21. Retrieved from http://ezproxy.library.ubc.ca/login?url=http://search.proquest.com/docview/207473353?accountid=14656

Pietikäinen, J., Pettersson, M., Bååth, E., Biologiska institutionen, Naturvetenskap, Science. . Lund University. (2005). Comparison of temperature effects on soil r espiration and bacterial and fungal growth rates. FEMS Microbiology Ecology, 52(1), 49-58. doi:10.1016/j.femsec.2004.10.002

Pohlabeln H, e. (2016). Exposure to pets and the risk of allergic symptoms during the first 2 years of life. - PubMed - NCBI. Ncbi.nlm.nih.gov. Retrieved 27 June 2016, from http://www.ncbi.nlm.nih.gov/pubmed/17982922

Reponen, T., Lockey, J., Bernstein, D. I., Vesper, S. J., Levin, L., Khurana Hershey, G. K.. . Lemasters, G. (2012). Infant origins of childhood asthma associated with specific molds. The Journal of Allergy and Clinical Immunology, 130(3), 639-644.e5. doi:10.1016/j.jaci.2012.05.030

R Core Team (2014). R: A language and environment for statistical computing. R Foundation for Statistical Computing, Vienna, Austria. URL http://www.R-project.org/.

Saadeh, D., Salameh, P., Baldi, I., & Raherison, C. (2013). Diet and allergic diseases among population aged 0 to 18 years: Myth or reality? Nutrients, 5(9), 3399-3423. doi:10.3390/nu5093399

Sbihi, H., Allen, R. W., Becker, A., Brook, J. R., Mandhane, P., Scott, J. A., & ... Brauer, M. (2015). Perinatal Exposure to Traffic-Related Air Pollution and Atopy at 1 Year of Age in a Multi-Center Canadian Birth Cohort Study. Environmental Health Perspectives, 123(9), 902-908. doi:10.1289/ehp.1408700

Tang, W., Kuehn, T. H., & Simcik, M. F. (2015). Effects of temperature, humidity and air flow on fungal growth rate on loaded ventilation filters. Journal of Occupational and Environmental Hygiene, 12(8), 525. doi:10.1080/15459624.2015.1019076

Takaro, T. K., Scott, J. A., Allen, R. W., Anand, S. S., Becker, A. B., Befus, A. D.. . CHILD study investigators. (2015). The canadian healthy infant longitudinal development (CHILD) birth cohort study: Assessment of environmental exposures. Journal of Exposure Science & Environmental Epidemiology, 25(6), 580. doi:10.1038/jes.2015.7

Talley, S., Coley, P., & Kursar, T. (2002). BMC Ecol, 2(1), 7. http://dx.doi.org/10.1186/1472-6785-2-7

Targonski, P. V., Persky, V. W., & Ramekrishnan, V. (1995). Effect of environmental molds on risk of death from asthma during the pollen season. The Journal of Allergy and Clinical Immunology, 95(5), 955-961. doi:10.1016/S0091-6749(95)70095-1

The conference Board of Canada. (2012). Lung Disease Imposes Major Costs on Canada's Economy. Conferenceboard.ca. Retrieved 16 May 2016, from http://www.conferenceboard.ca/press/newsrelease/12-03-15/lung_disease_imposes_major_costs_on_canada_s_economy.aspx

Wagenmakers, E. & Farrell, S. (2004). AIC model selection using Akaike weights. Psychonomic Bulletin & Review, 11(1), 192-196. http://dx.doi.org/10.3758/bf03206482

Wjst, M., Dold, S., Reitmeir, P., Stiepel, E., & Von Mutius, E. (1992). Month of birth and allergic disease at the age of 10. Clinical and Experimental Allergy : Journal of the British Society for Allergy and Clinical Immunology, 22(11), 1026-1031. doi:10.1111/j.1365-2222.1992.tb03032.x

Wu, P., Dupont, W. D., Griffin, M. R., Carroll, K. N., Mitchel, E. F., Gebretsadik, T., & Hartert, T. V. (2008). Evidence of a causal role of winter virus infection during infancy in early childhood asthma. American Journal of Respiratory and Critical Care Medicine, 178(11), 1123-1129. doi:10.1164/rccm.200804-579OC

Zhou, C., Baïz, N., Zhang, T., Banerjee, S., Annesi-Maesano, I., & EDEN Mother-Child Cohort Study Group. (2013). Modifiable exposures to air pollutants related to asthma phenotypes in the first year of life in children of the EDEN mother-child cohort study. BMC Public Health, 13, 506. doi:10.1186/1471-2458-13-506

Appendix A

Variables Code Book 2010-2013 Outcome variable at age of 3Y: Atopic status		
Meaning	Code	
Date of Birth		
DOB	CBIRTHCDQ2	
Skin Test		
This test was performed on the child"s:	CSKP3YQ	[1] Forearm [2] Back
Positive control (Histamine):	CSKP3YQ1a	(Numeric - Length: 4) Wheal width
	CSKP3YQ1b	Numeric - Length: 4) Wheal length
Negative control (Glycerin):	CSKP3YQ1a	(Numeric - Length: 4) Wheal width
	CSKP3YQ1b	Numeric - Length: 4) Wheal length
Alternaria Tenuis:	CSKP3YQ3a	(Numeric - Length: 4) Wheal width
	CSKP3YQ3b	Numeric - Length: 4) Wheal length
Cladosporium:	CSKP3YQ4a	(Numeric - Length: 4) Wheal width
	CSKP3YQ4b	Numeric - Length: 4) Wheal length
Penicillium Mixed:	CSKP3YQ5a	(Numeric - Length: 4) Wheal width
	CSKP3YQ5b	Numeric - Length: 4) Wheal length
Aspergillus fumigatus:	CSKP3YQ6a	(Numeric - Length: 4) Wheal width
	CSKP3YQ6b	Numeric - Length: 4) Wheal length
Cat Hair, Standardized:	CSKP3YQ7a	(Numeric - Length: 4) Wheal width

	CSKP3YQ7b	Numeric - Length: 4) Wheal length
Dog Epithelium:	CSKP3YQ8a	(Numeric - Length: 4) Wheal width
	CSKP3YQ8b	Numeric - Length: 4) Wheal length
D. Pteronyssinus:	CSKP3YQ9a	(Numeric - Length: 4) Wheal width
	CSKP3YQ9b	Numeric - Length: 4) Wheal length
D. Farinae:	CSKP3YQ10a	(Numeric - Length: 4) Wheal width
	CSKP3YQ10b	Numeric - Length: 4) Wheal length
Cockroach, German:	CSKP3YQ11a	(Numeric - Length: 4) Wheal width
	CSKP3YQ11b	Numeric - Length: 4) Wheal length
Trees Midwest:	CSKP3YQ12a	(Numeric - Length: 4) Wheal width
	CSKP3YQ12b	Numeric - Length: 4) Wheal length
Grass Mix:	CSKP3YQ13a	(Numeric - Length: 4) Wheal width
	CSKP3YQ13b	Numeric - Length: 4) Wheal length
Weeds:	CSKP3YQ14a	(Numeric - Length: 4) Wheal width
	CSKP3YQ14b	Numeric - Length: 4) Wheal length
Ragweed Mixed:	CSKP3YQ15a	(Numeric - Length: 4) Wheal width
	CSKP3YQ15b	Numeric - Length: 4) Wheal length
Peanut:	CSKP3YQ16a	(Numeric - Length: 4) Wheal width
	CSKP3YQ16b	Numeric - Length: 4) Wheal length
Milk, Whole Cow"s:	CSKP3YQ17a	(Numeric - Length: 4) Wheal width
	CSKP3YQ17b	Numeric - Length: 4) Wheal length
Egg White:	CSKP3YQ18a	(Numeric - Length: 4) Wheal width

	CSKP3YQ18b	Numeric - Length: 4) Wheal length
Soybean:	CSKP3YQ19a	(Numeric - Length: 4) Wheal width
	CSKP3YQ19b	Numeric - Length: 4) Wheal length
DATE OF TESTING:	CSKP3YQ20d	(DateTime - Length: 12)
Sex		
	CBIRTHCDQ2	[1] Male
		[2] Female
SES 18 WK		
Education mom	SES18WKQ1	[1] Less than high school
		[2] Some high school
		[4] Some college
		[7] Completed university
		[5] Completed college
		[8] Masters degree
		[3] Completed high school
		[9] PhD
		[6] Some university
		[10] Other
Education Dad	SES18WKQ3	[1] Less than high school
		[7] Completed university
		[2] Some high school
		[5] Completed college

		[8] Masters degree
		[3] Completed high school
		[4] Some college
		[6] Some university
		[9] PhD
		[10] Other
What is the best estimate of the total income, before taxes and deductions, of all household members, from all sources in the past 12 months.	SES18WKQ9	[1] $0 - $9,999
		[5] $40,000 - $49,999
		[9] $100,000 - $149,999
		[2] $10,000 - $19,999
		[6] $50,000 - $59,999
		[10] $150,000 or over
		[3] $20,000 - $29,999
		[7] $60,000 - $79,999
		[11] Prefer not to say
		[4] $30,000 - $39,999
		[8] $80,000 - $99,999
Cold		
Has baby had any colds between 3 and 6	CHLTH6MQ1	[1] Yes

months of age?		
		[0] No
Pet		
Have you had any FURRY pets living in your home during the last 3 months?	HENV6MQ8	[1] Yes
		[0] No
Exposure to second hand smoking		
Does anyone, at present, smoke AT baby"s home?	HENV6MQ20	[1] Yes
		[0] No
Has your baby been exposed to tobacco smoke AWAY from baby's home between 3 and 6 months of age?	HENV6MQ21	[1] Yes
		[0] No
Mold		
Are there visible signs of MOULD in the basement?	ENVRA3MQ25	[1] Yes
		[0] No
Air pollution		
	the average of NO2 concentration for the first six month of life	continuous

	for each subject	
[8888] Subject skipped the questionnaire [888] Not applicable [999] No response to this question [1]/[0] Inclusive selection (checkbox): [1-Yes]/[0-No]		